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Mathematical investigation of diabetically impaired ultradian oscillations in the glucose-insulin regulation*

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Abstract

We study the effect of diabetic deficiencies on the production of an oscillatory ultradian regime using a deterministic nonlinear model which incorporates two physiological delays. It is shown that insulin resistance impairs the production of oscillations by dampening the ultradian cycles. Four strategies for restoring healthy regulation are explored. Through the introduction of an instantaneous glucose-dependent insulin response, explicit conditions for the existence of periodic solutions in the linearised model are formulated, significantly reducing the complexity of identifying an oscillatory regime. The model is thus shown to be suitable for representing the effect of diabetes on the oscillatory regulation and for investigating pathways to reinstating a physiological healthy regime.

Keywords: Diabetes, Impaired ultradian rhythms, Four healthy regulation strategies, Delay differential equations, Stability analysis.

1. Introduction

Diabetes Mellitus is an illness which impairs the regulation of glucose and insulin blood levels. There are two main types: Type 1 diabetes (T1DM), which is an autoimmune disorder where the body destroys the β -cells in the pancreas, almost completely removing the body's ability to secrete insulin [23], and type 2 diabetes (T2DM), where the muscle cells start to become insulin resistant, hindering the body's ability to utilise glucose correctly [23]. It can be the cause of many other long term problems, such as, retinopathy, cardiovascular disease, nephropathy and neuropathy [5], and is expected to be the 7th leading cause of death by the year 2030 [20].

Within this regulation, both rapid (period \approx 6-15 minutes) and ultradian (period \approx 80-180 minutes) oscillations of insulin have been observed [29], along with glucose

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oscillations (period \approx 80-150 minutes) that are tightly coupled to the insulin oscillations of similar period [30]. This work solely focuses on the modelling of these ultradian oscillations, which were first discovered in [10] and have been observed during fasting, meal ingestion, continuous enteral nutrition, and under a constant glucose infusion [33] (the condition upon which we will perform our analysis). For a review of ultradian oscillations, readers are directed to [26, 33]. In [17, 35, 37] mathematical analysis of the dynamics of models taking into account physiological time delays suggested that the delayed feedback loop between glucose and insulin can account for the ultradian rhythms within the system, without the technical need for an internal pulsatile insulin pacemaker.

As was highlighted in [24], insulin resistance leads to a lack of control of the ultradian rhythms in the glucose-insulin system, with the main effect of dampening the oscillations. This suggests that they may be crucial in the maintenance of normal glucose homeostasis [36]. Therefore, we adopt the presence and the accurate tuning of ultradian rhythms as a criterion for healthy glucose regulation, and ask the following question:

What is the effect of reduced insulin production and/or sensitivity on the ultradian rhythms in an individual and what mechanisms can be used to restore the ultradian oscillatory regime to an acceptable physiological behaviour?

To answer this question, we propose a mathematical model which is adapted from the work of Sturis et al.[35] and then developed by several authors [7, 11, 16, 17, 39]. Our focus then shifts to the mathematical description of the impact of deficiencies in the glucose-insulin regulatory system on: (i) the production of an accurate oscillatory regulation and (ii) the maintenance of a physiologically acceptable average blood glucose level. We then devise four strategies in an attempt to restore objectives (i) and (ii).

Of the previous glucose-insulin models, one of particular note is a two-delay model of Kissler et al.[14], featuring Michaelis-Menten dynamics for quantifying the insulin degradation, which is used to investigate personalised treatment options for diabetics, while maintaining oscillations. For reviews of many more of the key models relating to the glucose-insulin system, see [19] and [25].

In view of the recent clinical debate regarding the potential role of hyperinsulinemia in aggravating insulin resistance [27], it appears of crucial importance to identify mechanisms which allow to keep both glucose and insulin levels within a physiologically acceptable range. Over the years, there has been much speculation that reducing insulin degradation may be used to treat T2DM [6, 21], and in Maianti et al. [18], it was shown that acute inhibition of insulin degradation enzyme (IDE) in mice led to substantially improved glucose tolerance. Hence it was hypothesized that IDE could be used as a therapeutic strategy to treat T2DM. However, in the usage of previous models, the insulin degradation rate has often been assumed to be constant even for varying diabetic states. Therefore, we note that when dealing with insulin therapies relating to insulin resistance, it is important to adjust insulin degradation in order to

avoid too high levels, and so we look to use insulin degradation to stabilise the glucose levels as one of our strategies, and as a bifurcation parameter to reintroduce an oscillatory regime as another.

In healthy subjects, experiments in isolated pancreatic islets have shown that insulin is secreted (in response to elevated blood glucose) in two phases: a rapid initial release of preformed insulin, which only lasts a few minutes [1, 3, 22], followed by a more sustained component, in which synthesis and release of the hormone is increased [1, 3]. In T2DM, it is well known that this initial release is reduced [32] (for a more in-depth look at the dynamics of insulin secretion, see [31]). By looking at this rapid response as an instantaneous glucose-dependent insulin release, we investigate the effect this has on the existence of periodic solutions in the linearised model.

In summary, the purpose of this paper is to understand the effect of diabetic parameters on the onset of the oscillatory regime and design four strategies for restoring healthy regulation. The work is divided as follows. The model is presented in Section 2. In Section 3, local stability analysis is used to study the effect of insulin resistance on the location and generation of the oscillations. Section 4 is devoted to strategies which can be used to restore glucose levels or oscillations. In Section 5, we formulate new conditions for the presence of periodic solutions in the linearised system where an instantaneous glucose-dependent insulin secretion is taken into account. Physiological implications are then discussed, along with final remarks and perspectives.

2. The two-delay model

The model proposed (based on the framework represented in Figure 1) is given by the following system of differential delay equations with two delays

$$\begin{aligned}\dot{G} &= G_{in} - f_2(G) - \beta f_3(G) f_4(I) + \gamma f_5(I(t - \tau_2)), \\ \dot{I} &= I_{in} + \alpha f_1(G(t - \tau_1)) - d_i(\alpha, \beta) I,\end{aligned}\tag{1}$$

Here $G(t)$ and $I(t)$ represent plasma glucose and plasma insulin concentrations in mg/dl and mU/l respectively.

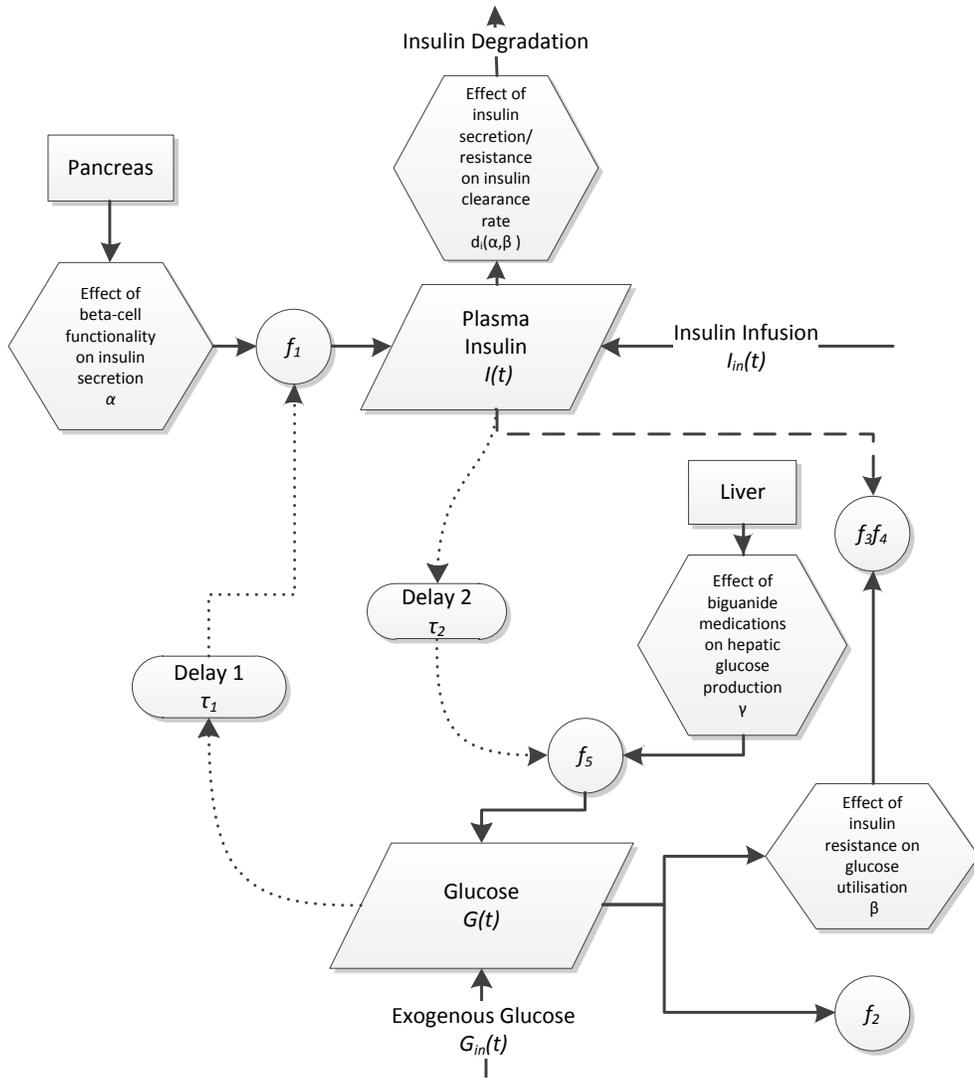


Figure 1: Flow diagram for model (1).

The relevant features of the model can be summarised as follows.

$\alpha f_1(G(t - \tau_1))$: Insulin production. A delay τ_1 is present in this process. It accounts for the time lag, in minutes, between when high glucose levels trigger the *production* of insulin within the pancreas and when it becomes available [17]. Clinical experiments have provided a time range of [5, 20] minutes for this reaction. The parameter α modulates this secretion, with low levels being typical of T1DM.

$f_2(G)$: Insulin-independent glucose utilisation, mainly by the brain.

$\beta f_3(G) f_4(I)$: Insulin-dependent glucose utilisation, by the muscles. Values of $\beta < 1$ indicate a reduced capacity of utilising insulin to degrade glucose, also called insulin resistance, which is seen in T2DM.

$\gamma f_5(I(t - \tau_2))$: Glucose production by the liver. The delay in this reaction, denoted by τ_2 , denotes the time between hepatic glucose production and insulin stimulation and is typically between 20 and 50 minutes [17]. This production is controlled by the parameter γ , to account for the effect of biguanide medications which act by lowering it to keep glucose levels low [12].

$d_i(\alpha, \beta)$: Combined rate of degradation of insulin, especially by the liver and kidneys. In Section 4, we consider it as a combination of natural (for example, exercise [38]) and artificial (for example, through use of Rosiglitazone [13]) mechanisms, and as a function of α and β to investigate how it can be used to compensate for the effects of a reduced insulin secretion (α) and/or an increased insulin resistance (β) on an appropriate oscillatory regime.

Typically f_3 is taken as a linear function of G , while the functions f_1, f_2, f_4 and f_5 are chosen as sigmoidal functions. Here, we represent these functions in terms of Hill functions,

$$f_1 = \frac{R_m(G/V_g)^{h_1}}{(G/V_g)^{h_1} + k_1^{h_1}}, \quad f_2 = \frac{U_b(G/V_g)^{h_2}}{(G/V_g)^{h_2} + k_2^{h_2}}, \quad f_3 = C_3 \frac{G}{V_g},$$

$$f_4 = U_0 + (U_m - U_0) \frac{[(1/V_i + 1/(Et_i))I]^{h_4}}{[(1/V_i + 1/(Et_i))I]^{h_4} + k_4^{h_4}}, \quad f_5 = R_p \frac{(I/V_p)^{h_5}}{(I/V_p)^{h_5} + k_5^{h_5}},$$

as defined by [11]. This gives the advantage of introducing new parameters in the model which bear physiological meaning (a list of which can be found in Tables 1 and 2), and hence allows for more adequate modelling of the underlying physiological dynamics of the glucose-insulin system [11]. These values were selected in [11] to ensure the system produces an oscillatory regime in a physiologically suitable range for a non-diabetic patient. The functions are all strictly positive and f_1, f_2, f_4 are increasing while f_5 is decreasing. Here the parameters α and β play a crucial role in modelling the capacity of an individual to produce insulin or use it to degrade glucose, respectively. Values of $\alpha = \beta = \gamma = 1$ represent an optimal non-diabetic patient. Therefore, a value of $\alpha < 1$ represents a reduced insulin production capability, which is seen in T1DM [23] (as well as after the onset of T2DM [27]). A value greater than 1 implies an increased insulin production capacity, observed in the very early stages of T2DM (although the reason for its occurrence is debated [27]). Likewise, if β is smaller than 1, this indicates a reduced insulin-dependent glucose utilisation which is typical of insulin resistance and related to both T1DM and T2DM [8]. A value greater than 1 represents an increased sensitivity to insulin, which can pose the risk of hypoglycaemia in T1DM. Finally, values of $\gamma < 1$ represent a reduced glucose hepatic production which can result from the usage of drugs such as Metformin [12], while $\gamma = 1$ corresponds to a typical non-diabetic production. For these reasons, the coefficients α , β and γ are named the *diabetic parameters* throughout this paper.

Our previous analysis focused on system (1) for an optimal non-diabetic patient ($\alpha = \beta = \gamma = 1$ and $I_{in} = 0$) [11]. The constant value of G_{in} is typically between 1 -

Hill coefficient	Value	Hill coefficient	Value
h_1	2	k_1	5830
h_2	1.8	k_2	103.5
h_4	1.5	k_4	80
h_5	-8.5	k_5	26.72

Table 1: Values used for the Hill coefficients h_i, k_i , taken from [11].

Constant	Value	Units	Constant	Value	Units
R_m	210	min	V_i	11	l
V_g	10	l	E	0.2	l/min
U_b	72	mg/min	t_i	100	min
C_3	1000	mg/l	R_g	180	mg/min
U_0	40	mg/min	V_p	3	l
U_m	940	mg/min	G_{in}	1.35	mg/dl min

Table 2: Parameters used in model (1). They were originally determined by fitting the functions $f_1 - f_5$ to published clinical experiments of individual subsystems (see [35] and references therein).

3 mg/dl min, a range where ultradian oscillations have been observed [33]. The joint role of the physiological delays in producing oscillations in the healthy case has already been highlighted [11, 16, 35]. Indeed, for any $\tau_1 > 0$, there exists a τ_2 such that the system undergoes a supercritical Hopf bifurcation at the point (τ_1, τ_2) . This situation is illustrated in Figure 2, where the threshold curve corresponds to the points where the system possesses a pair of pure imaginary eigenvalues.

3. Local stability analysis and the effect of insulin resistance on ultradian oscillations

In this section, we investigate the effect of the diabetic parameter β on the steady state (G^*, I^*) of model (1), which is governed by the following system of algebraic equations

$$G_{in} - f_2(G^*) - \beta f_3(G^*)f_4(I^*) + \gamma f_5(I^*) = 0, \quad (2)$$

$$I_{in} + \alpha f_1(G^*) - d_i(\alpha, \beta)I^* = 0. \quad (3)$$

To match physiological values, the values for the steady state should fit the ranges $90 < G^* < 120$ and $25 < I^* < 40$ respectively [35]. Given the assumptions on the functions and the parameters of the model, it can be shown that this system has a unique solution (see e.g. [2]). The dependence upon β can be made more explicit in the following way. Differentiating implicitly equations (2) and (3) with respect to β leads to the following expressions

$$\begin{aligned} -f_2'(G^*)G_\beta^* - f_3(G^*)f_4(I^*) - \beta (f_3'(G^*)f_4(I^*)G_\beta^* + f_3(G^*)f_4'(I^*)I_\beta^*) + \gamma f_5'(I^*)I_\beta^* &= 0, \\ \alpha f_1'(G^*)G_\beta^* - d_i(\alpha, \beta)_\beta I^* - d_i(\alpha, \beta)I_\beta^* &= 0, \end{aligned}$$

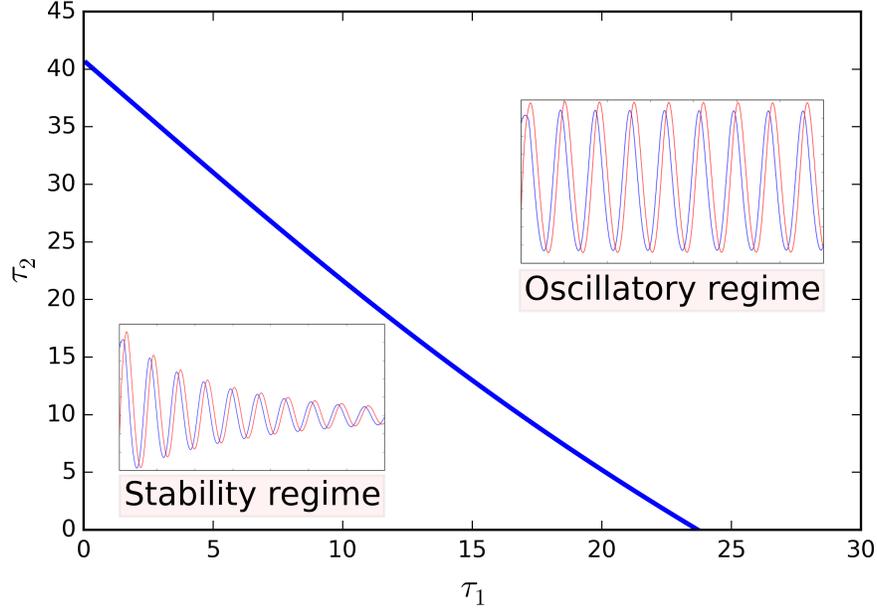


Figure 2: Curve of Hopf bifurcations in the optimal non-diabetic case $\alpha = \beta = \gamma = 1$, with $d_i = 0.06$ and $G_{in} = 1.35$ mg/dl.

where the β subscript stands for the derivative. In matrix form, these can be written as

$$\begin{pmatrix} -A & -(B+C) \\ D & -d_i(\alpha, \beta) \end{pmatrix} \begin{pmatrix} G_\beta^* \\ I_\beta^* \end{pmatrix} = \begin{pmatrix} f_3(G^*)f_4(I^*) \\ d_i(\alpha, \beta)_\beta I^* \end{pmatrix}, \quad (4)$$

where we have introduced the following positive β -dependent quantities

$$A = f_2'(G^*) + \beta f_3'(G^*)f_4(I^*), \quad B = \beta f_3(G^*)f_4'(I^*), \quad C = -\gamma f_5'(I^*), \quad D = \alpha f_1'(G^*),$$

with the prime $'$ standing for the derivative. The dependence of these functions on β is illustrated in Figure 3.

Hence

$$\begin{pmatrix} G_\beta^* \\ I_\beta^* \end{pmatrix} = \frac{1}{\Delta} \begin{pmatrix} d_i(\alpha, \beta)_\beta I^*(B+C) - d_i(\alpha, \beta)f_3(G^*)f_4(I^*) \\ -Df_3(G^*)f_4(I^*) - Ad_i(\alpha, \beta)_\beta \end{pmatrix}, \quad (5)$$

with

$$\Delta = Ad_i(\alpha, \beta) + D(B+C) > 0.$$

The location of the steady state of the system is linked to the level of insulin resistance and the clearance rate. Assuming no correlation between insulin degradation and insulin resistance, i.e. assuming d_i is constant, the effect of reduced insulin regulation capacity on the steady state (G^*, I^*) of system (1) is depicted in Figure 4. This picture

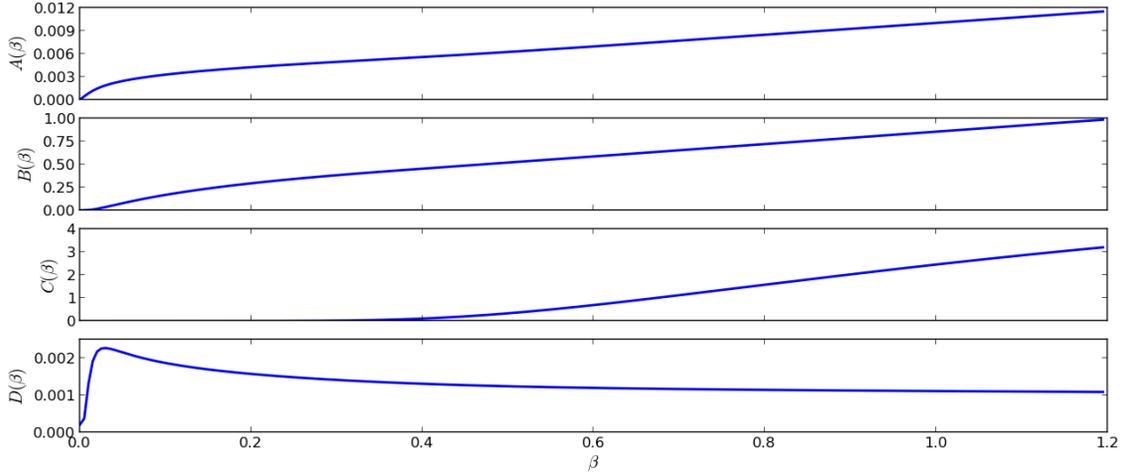


Figure 3: Graphs of the functions $A(\beta), B(\beta), C(\beta), D(\beta)$ for parameter values from Tables 1 and 2, with $d_i = 0.06$ and $I_{in} = 0$.

is already instructive. As expected, reducing insulin production ($\alpha < 1$) leads to lower insulin and higher glucose levels. However, it is important to note that introducing insulin resistance (or equivalently decreasing β) leads to both higher glucose and insulin levels. An investigation of strategies for improving these by altering $d_i(\alpha, \beta)$ will be performed in Section 4.

We now look at the effect of β on the production of oscillations. The linearisation of system (1) about (G^*, I^*) is given by

$$\begin{pmatrix} \dot{u} \\ \dot{v} \end{pmatrix} = \begin{pmatrix} -A & -B \\ 0 & -d_i(\alpha, \beta) \end{pmatrix} \begin{pmatrix} u(t) \\ v(t) \end{pmatrix} + \begin{pmatrix} 0 & 0 \\ D & 0 \end{pmatrix} \begin{pmatrix} u(t - \tau_1) \\ v(t - \tau_1) \end{pmatrix} + \begin{pmatrix} 0 & -C \\ 0 & 0 \end{pmatrix} \begin{pmatrix} u(t - \tau_2) \\ v(t - \tau_2) \end{pmatrix}, \quad (6)$$

A complex exponential solution $e^{\lambda t}$ of system (6) exists if and only if λ satisfies the following characteristic quasipolynomial

$$(\lambda + A)(\lambda + d_i(\alpha, \beta)) + D [B e^{-\lambda \tau_1} + C e^{-\lambda(\tau_1 + \tau_2)}] = 0, \quad (7)$$

where it is important to note that A, B, C, D are functions of β . We now show that the characteristic equation (7) implies that the introduction of insulin resistance leads to the loss of oscillations, that is we wish to prove that if we set $\lambda = \eta + i\phi$, where η and ϕ are assumed to depend on β , then

$$\left. \frac{d\eta}{d\beta} \right|_{\beta=1} > 0.$$

Splitting the real and imaginary parts of (7) and differentiating with respect to β , we get expressions of the type

$$\frac{d\phi}{d\beta} c = \frac{d\eta}{d\beta} a + b, \quad \frac{d\phi}{d\beta} a = -\frac{d\eta}{d\beta} c - d, \quad (8)$$

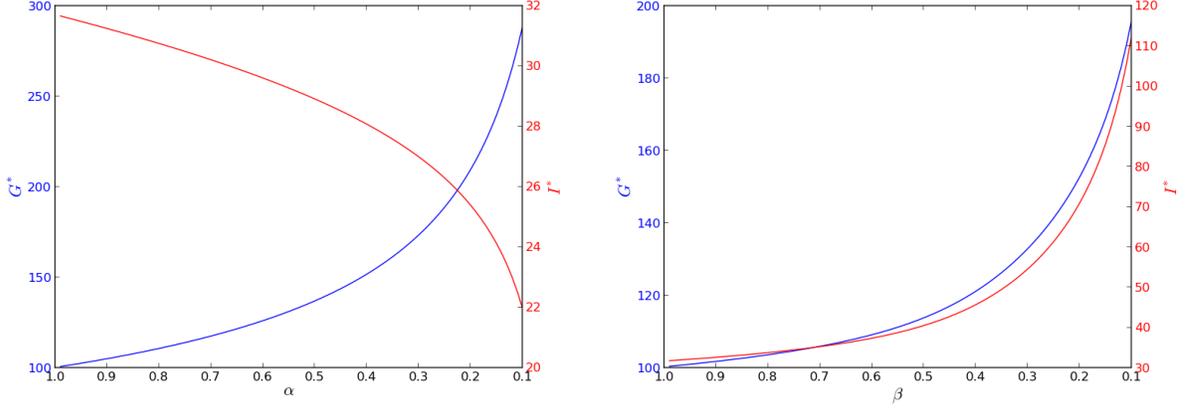


Figure 4: Effect on the steady state of reducing (left) insulin production and (right) insulin-dependent glucose utilisation, for $d_i = 0.06$. The glucose and insulin steady states are represented by the blue and red curves, respectively.

where we introduced the following definitions

$$\begin{aligned}
 a &= 2\eta + A + d_i - \tau_1 e^{-\eta\tau_1} BD \cos \phi \tau_1 - (\tau_1 + \tau_2) e^{-\eta(\tau_1+\tau_2)} CD \cos \phi (\tau_1 + \tau_2), \\
 b &= A_\beta \eta + d'_i \eta + (d_i A)_\beta + e^{-\eta\tau_1} \cos \phi \tau_1 (BD)_\beta + e^{-\eta(\tau_1+\tau_2)} \cos \phi (\tau_1 + \tau_2) (CD)_\beta, \\
 c &= 2\phi + \tau_1 \sin \phi \tau_1 B D e^{-\eta\tau_1} + (\tau_1 + \tau_2) \sin \phi (\tau_1 + \tau_2) C D e^{-\eta(\tau_1+\tau_2)}, \\
 d &= \phi (A_\beta + d'_i) - e^{-\eta\tau_1} \sin \phi \tau_1 (BD)_\beta - e^{-\eta(\tau_1+\tau_2)} \sin \phi (\tau_1 + \tau_2) (CD)_\beta.
 \end{aligned} \tag{9}$$

Rearranging equations (8) and eliminating $\frac{d\phi}{d\beta}$ leads to an explicit expression for $\frac{d\eta}{d\beta}$ of the form

$$\frac{d\eta}{d\beta} = -\frac{ab + cd}{a^2 + c^2} \tag{10}$$

We then obtain the following:

Proposition 1. *Let $\lambda(\beta) = \eta(\beta) + i\phi(\beta)$ be a solution of the characteristic equation (7). Then $\frac{d\eta}{d\beta} > 0$ if and only if $ab + cd < 0$, with a, b, c, d as defined in (9).*

We now assume that an oscillatory regulation takes place when $\beta = 1$, which is when the system is in normal regulation. We consider the case on the threshold curve, that is $\lambda|_{\beta=1} = (\eta + i\phi)|_{\beta=1} = i\omega$, where $\omega > 0$ satisfies a transcendental equation. Indeed, setting $\lambda = i\omega$ in (7) and separating the real and imaginary parts leads to the following equation

$$\cos(\tau_2\omega) = \frac{(\omega^2 + A^2)(\omega^2 + d_i^2) - D^2(B^2 + C^2)}{2BCD^2}, \tag{11}$$

where ω can be seen as a function of τ_1 through the following transcendental equation

$$(\omega^2 + A^2)(\omega^2 + d_i^2) + D^2(B^2 - C^2) + 2BD((Ad_i - \omega^2) \cos(\tau_1\omega) - \omega(A + d_i) \sin(\tau_1\omega)) = 0. \quad (12)$$

It can be seen from Figure 5 that $\frac{d\eta}{d\beta}|_{\beta=1} > 0$ when τ_1 is within a physiological range, between 5 and 20 minutes. This implies that η decreases when β decreases from 1 or, in other words, that the oscillations are lost as β decreases from 1. The overall effect of β on the production of oscillations can then be seen in Figure 6. As an example, the distribution of eigenvalues λ in the prototypical case $\tau_1 = 6$ and $\tau_2 = 36$ is depicted in Figure 7, for cases with ($\beta = 1$) and without ($\beta = 0.8$) oscillations.

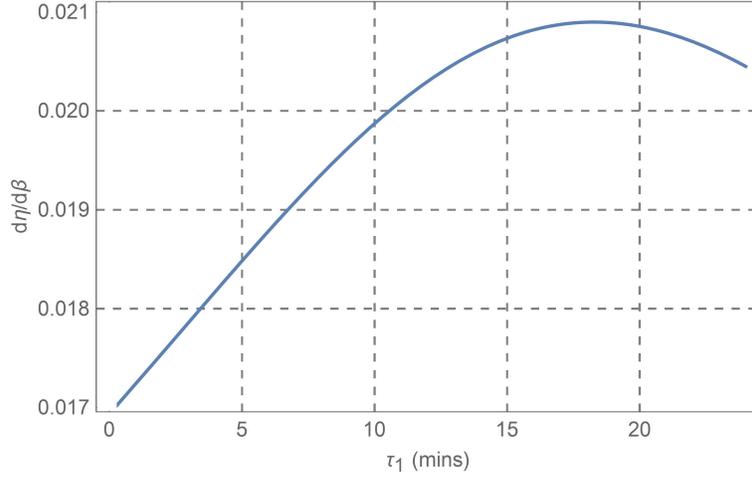


Figure 5: The derivative $\frac{d\eta}{d\beta}$ as a function of τ_1 , with parameter values from Tables 1 and 2, with $d_i = 0.06$, $I_{in} = 0$ and $\beta = 1$. Typical values for τ_1 are to be chosen between 5 and 20 minutes.

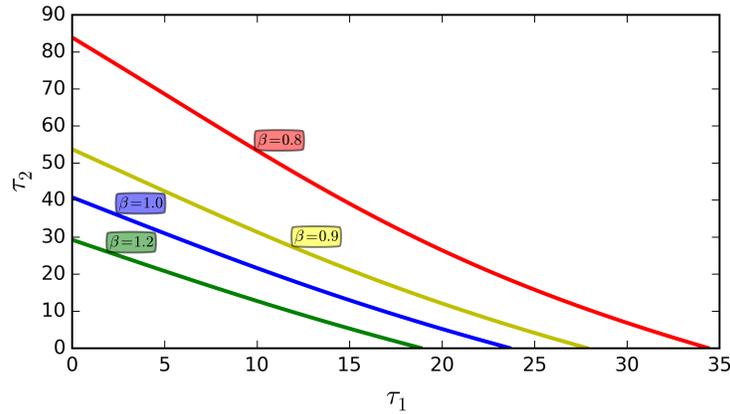


Figure 6: Effect of insulin resistance on the curve of Hopf bifurcations in the (τ_1, τ_2) space.

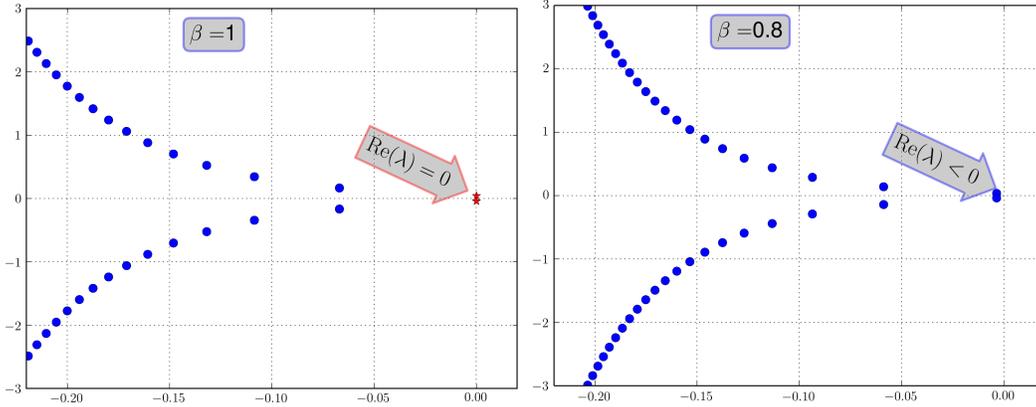


Figure 7: Eigenvalues of the linearised system for $\tau_1 = 6$, $\tau_2 = 36$ and $d_i = 0.06$, when $\beta = 1$ (left) and $\beta = 0.8$ (right).

4. Strategies for stabilising glucose levels and restoring oscillations

We now investigate strategies allowing the stabilisation of the basal glucose level and/or the restoration of oscillations using the insulin degradation or insulin infusion as a bifurcation parameter. As stated in Section 2, $d_i(\alpha, \beta)$ is viewed as a combination of natural and artificial processes which regulate the clearance of insulin. Indeed, under the assumption that the insulin degradation rate is adjusted in a continuous way, proportionally to the insulin levels, this effect can be incorporated into $d_i(\alpha, \beta)$. Our analysis for the stabilisation processes makes use of equations (2) and (3) for the steady state (G^*, I^*) , as given in Section 3. In the optimal non-diabetic case $\alpha = \beta = \gamma = 1$, the current choice of parameters from Tables 1 and 2 gives a value of $G^* \approx 97.87$ mg/dl, which we use as the reference value.

The effect of this stabilisation mechanism on the generation of an oscillatory regime is also investigated as follows. It is known that for all values of A, B, C, D, $d_i(\alpha, \beta)$, and any fixed τ_1 , there exists a $\tau_2^*(\tau_1)$ such that the characteristic equation (7) undergoes a supercritical Hopf bifurcation in the (τ_1, τ_2) space [16]. If we then suppose that an individual has fixed secretion time delays (here we use $\tau_1 = 6$ and $\tau_2 = 36$), then for a fixed pair (α, β) one can compute the point of Hopf bifurcation $\tau_2^*(6)$ using formulas (11) and (12). Since every $\tau_2 > \tau_2^*(6)$ will lead to an oscillatory regime (see Figure 2), this provides an easy way to verify whether the pair (α, β) is oscillatory, and hence allows to decide whether specific values of α and β for a given individual (with fixed τ_1 and τ_2) lead to an oscillatory regime.

4.1. Using insulin injections to stabilise the glucose level G^*

In current practice, insulin injections are used in the treatment plan for all Type 1 diabetics, as well as for some with T2DM [5] (although the use of insulin therapy in the initial treatment for T2DM is debated [27]). We assume here that a continuous insulin infusion may allow to stabilise the basal glucose level. Indeed, since the steady state (G^*, I^*) satisfies equations (2) and (3), it is easily computed that in order to keep G^*

constant, for fixed $G_{in}, \alpha, \beta, \gamma$, one can solve equation (2) to obtain I^* while equation (3) gives

$$I_{in} = d_i(\alpha, \beta)I^* - \alpha f_1(G^*). \quad (13)$$

Using the algorithm detailed above, we determine whether each (α, β) , with I_{in} as defined by (13) and $d_i = 0.06$, leads to an oscillatory regime. The result is shown in Figure 8. For physiological accuracy, only values of (α, β) where $I_{in} > 0$ were considered. It can be seen that insulin injections are indeed able to stabilise the basal glucose level for a vast range of diabetic states. However, in the case when $\gamma = 1$, oscillations are only restored for a small range of α, β . This range was further reduced when γ was decreased.

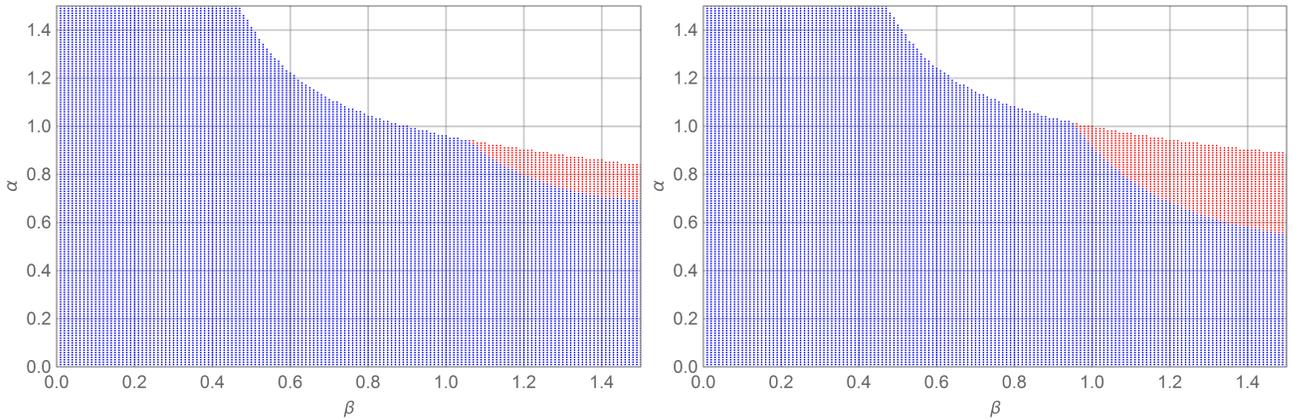


Figure 8: Oscillatory region (in red) in the α, β domain for $d_i = 0.06$ with I_{in} as defined by (13) with $\gamma = 0.7$ (left) and $\gamma = 1$ (right). The white region represents values of (α, β) where the resulting value of I_{in} is negative.

4.2. Reducing hepatic glucose production to stabilise the glucose level G^*

Inhibiting hepatic glucose production can also be seen as a mechanism for reducing glucose levels, as employed by several medications occurring in the treatment of T2DM [12]. Let us consider a situation where insulin resistance is present, $\beta < 1$, and investigate under which circumstances the reduction of hepatic glucose allows to keep the value of G^* constant. Assuming d_i and I_{in} are fixed, (2) and (3) can be rearranged to obtain the stabilising value of γ ,

$$\gamma = \frac{G_{in} - f_2(G^*) - \beta f_3(G^*) f_4\left(\frac{I_{in} + \alpha f_1(G^*)}{d_i}\right)}{f_5\left(\frac{I_{in} + \alpha f_1(G^*)}{d_i}\right)}. \quad (14)$$

It can be seen in (14) that there is a linear relationship between β and γ in compensating insulin resistance by reducing hepatic glucose production. Applying the algorithm described previously, one can assess whether the resulting choice leads to an oscillatory regime. The result is illustrated in Figure 9.

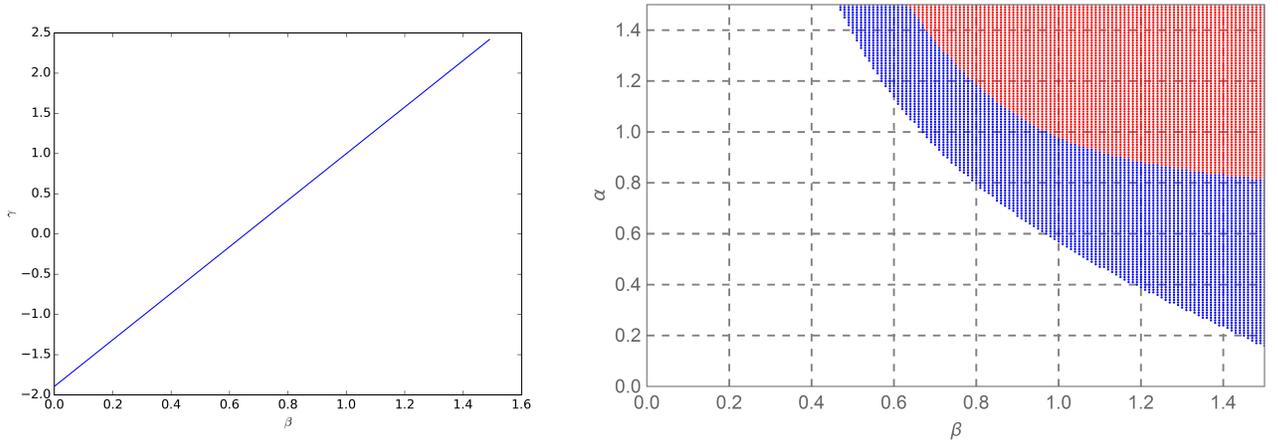


Figure 9: Value of γ that allows to stabilise $G^* = 97.87$ mg/dl (left, for $\alpha = 1$) and the resulting oscillatory region (in red, right) in the α, β domain for γ defined by (14), with $d_i = 0.06$, $I_{in} = 0$. The white region corresponds to negative values of γ .

4.3. Altering insulin degradation to stabilise the glucose level G^*

As mentioned in Section 4.1, since the steady state (G^*, I^*) satisfies equations (2) and (3), it can be easily computed that

$$G_{in} - f_2(G^*) - \beta f_3(G^*) f_4(I^*) + \gamma f_5(I^*) = 0, \quad (15)$$

$$I^* = \frac{I_{in} + \alpha f_1(G^*)}{d_i(\alpha, \beta)}. \quad (16)$$

Using (15) and (16), with fixed α , we can determine the function $d_i(\alpha, \beta)$ which stabilises the glucose basal level to 97.87 mg/dl and the resulting insulin basal level, I^* . These can be seen in Figure 10.

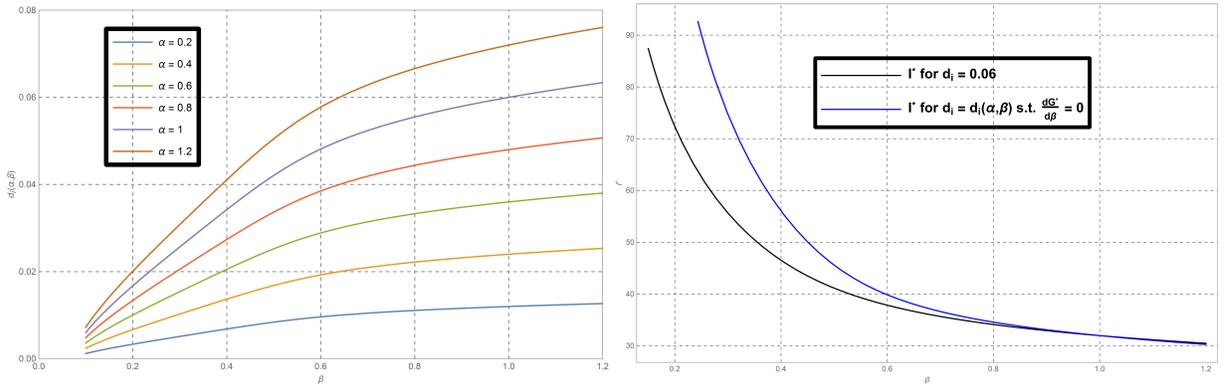


Figure 10: Clearance rate which allows to stabilise $G^* = 97.87$ mg/dl and the resulting I^* when $d_i(1, 1) = 0.06$ and $I_{in} = 0$.

The graphs clearly show that in the case of moderate insulin resistance ($\beta \in [0.6, 1]$), it is possible to keep both the glucose and insulin basal levels relatively unchanged by altering the insulin clearance rate.

It is readily seen that this strategy can be applied in the case of limited insulin resistance.

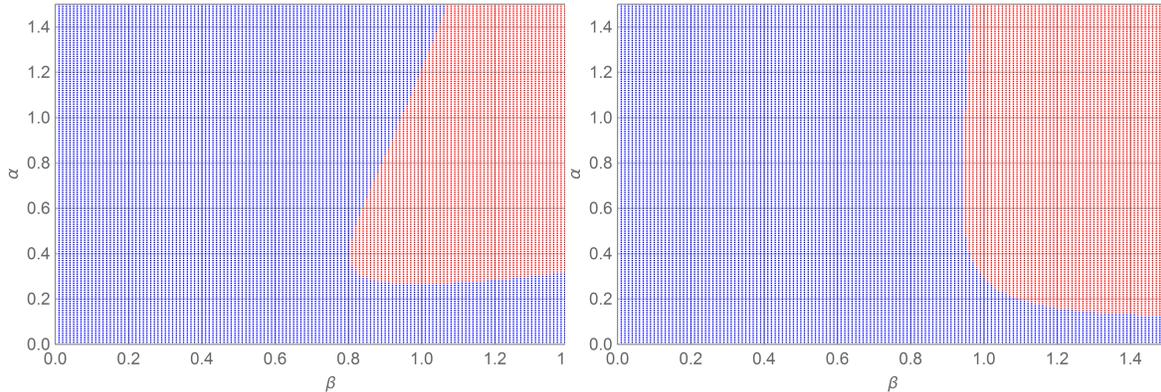


Figure 11: Oscillatory region (in red) in the α, β domain for $d_i = 0.06$ (left) and $d_i(\alpha, \beta)$ defined by (15), with $I_{in} = 0$.

4.4. Reintroducing oscillations

The final strategy is to focus primarily on the reintroduction of an oscillatory regime. To this end, we use d_i as a bifurcation parameter to assess whether altering insulin clearance may be used for this purpose. However, a Hopf bifurcation has only been shown to occur in the (τ_1, τ_2) space, and so we use the algorithm outlined previously in order to determine whether the system oscillates for a given (α, β, d_i) , and hence obtain the oscillatory region in the (α, β, d_i) space (shown in Figure 12). We also verify that the resulting fasting glucose levels fall within an acceptable physiological range. It can be seen from Figure 12 that changing d_i is considerably more effective for restoring oscillations for large variations of α than β . Indeed, for values of $\beta < 0.9$, d_i cannot be used to restore the oscillatory regime of the system and keep the fasting glucose levels within an acceptable range.

5. Instantaneous insulin response and periodic solutions in the linear system

In this section, we derive explicit conditions for the existence of sinusoidal solutions for linear systems with two delays

$$\dot{x}(t) = a_1x(t) + a_2y(t) + a_3y(t - \tau_2), \quad \dot{y}(t) = a_4x(t) + a_5y(t) + a_6x(t - \tau_1). \quad (17)$$

The purpose of this derivation is twofold. On one hand, contrary to the case $a_4 = 0$ where the solution of a transcendental equation is required, we show that conditions can be formulated when $a_4 \neq 0$ by investigating the roots of a cubic polynomial. On

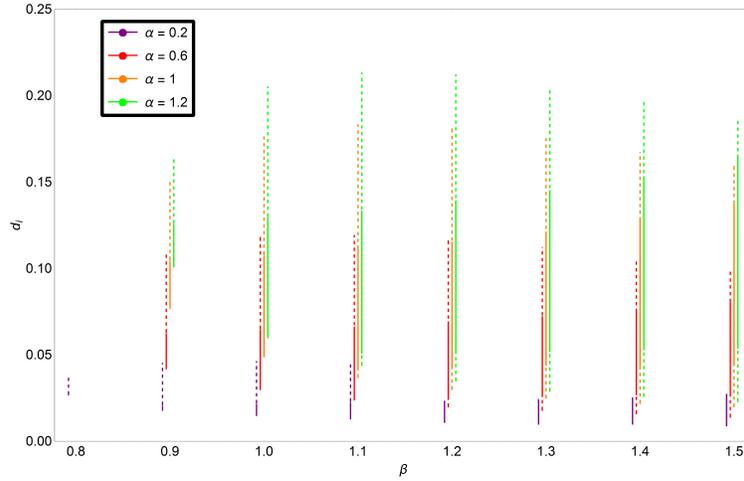


Figure 12: Oscillating regions in the α, β, d_i domain. The solid sections represent the values of d_i for which both oscillations occur, and the fasting glucose levels lie within an acceptable range (70-109 mg/dl).

the other hand, in the context of model (1), the introduction of the coefficient a_4 would correspond to an instantaneous glucose-dependent insulin secretion. Hence our conditions provide a qualitative description of the effect of such an insulin contribution.

We assume here that $a_3, a_6 \neq 0$ to ensure the dependence upon the two delays is preserved and postulate the form of the solution as

$$x(t) = A_1 \cos(\omega t) + A_2 \sin(\omega t), \quad y(t) = B_1 \cos(\omega t) + B_2 \sin(\omega t). \quad (18)$$

Given that the system is linear, we impose that $x(t)$ and $y(t)$ are normalised such that $A_1^2 + A_2^2 = 1$, $B_1^2 + B_2^2 = r^2$, $r > 0$. Hence we set

$$A_1 = \cos \phi, \quad A_2 = \sin \phi, \quad B_1 = r \cos \theta, \quad B_2 = r \sin \theta. \quad (19)$$

Substituting (18) into (17), one obtains the following system

$$\begin{aligned} \cos(\tau_2 \omega) &= -\frac{1}{a_3 r} [a_2 r + a_1 \cos z + \omega \sin z], & \sin(\tau_2 \omega) &= \frac{1}{a_3 r} [a_1 \sin z - \omega \cos z], \\ \cos(\tau_1 \omega) &= -\frac{1}{a_6} [a_4 + a_5 \cos z - r \omega \sin z], & \sin(\tau_1 \omega) &= -\frac{r}{a_6} [a_5 \sin z + \omega \cos z], \end{aligned} \quad (20)$$

given that $a_3, a_6 \neq 0$, with $z = \theta - \phi$. These lead to the following conditions

$$\omega^2 + 2a_2 r (\omega \sin z + a_1 \cos z) + a_1^2 + r^2 (a_2^2 - a_3^2) = 0, \quad (21)$$

$$r^2 \omega^2 + 2a_4 r (a_5 \cos z - \omega \sin z) + r^2 a_5^2 + a_4^2 - a_6^2 = 0, \quad (22)$$

Here we focus exclusively on the generic case where $a_2, a_4, a_1 + a_5 \neq 0$. Conditions when $a_2 = a_4 = 0$ have been discussed, for example in [28] using degree theory. We do not make use of a rational transformation to bring the transcendental equation into a

polynomial problem (as done, for example in [9, 34]). In the generic case, one can solve (21) and (22) for $\sin z$ and $\cos z$ and upon using that $\cos^2 z + \sin^2 z = 1$, we obtain a cubic polynomial for $\rho = \omega^2$,

$$b_3\rho^3 + b_2\rho^2 + b_1\rho + b_0 = 0, \quad (23)$$

with

$$\begin{aligned} b_0 &= (a_1^2 a_4 a_5 - a_1 a_2 a_4^2 - a_1 a_2 a_5^2 r^2 + a_1 a_2 a_6^2 + a_2^2 a_4 a_5 r^2 - a_3^2 a_4 a_5 r^2)^2, \\ b_1 &= a_1^4 a_4^2 - 2a_1^3 a_2 a_4 a_5 r^2 + 2a_1^2 a_2^2 a_5^2 r^4 - 2a_1^2 a_2^2 a_6^2 r^2 + 2a_1^2 a_2 a_4^3 + 2a_1^2 a_2 a_4 a_5^2 r^2 \\ &\quad - 2a_1^2 a_2 a_4 a_6^2 - 2a_1^2 a_3^2 a_4^2 r^2 + 2a_1^2 a_4^2 a_5^2 - 2a_1 a_2^3 a_4 a_5 r^4 - 8a_1 a_2^2 a_4^2 a_5 r^2 + 2a_1 a_2 a_3^2 a_4 a_5 r^4 \\ &\quad - 2a_1 a_2 a_4^3 a_5 - 2a_1 a_2 a_4 a_5^3 r^2 + 2a_1 a_2 a_4 a_5 a_6^2 + a_2^4 a_4^2 r^4 + 2a_2^3 a_4^3 r^2 + 2a_2^3 a_4 a_5^2 r^4 \\ &\quad - 2a_2^3 a_4 a_6^2 r^2 - 2a_2^2 a_3^2 a_4^2 r^4 + a_2^2 a_4^4 - 2a_2^2 a_4^2 a_6^2 + a_2^2 a_5^4 r^4 - 2a_2^2 a_5^2 a_6^2 r^2 + a_2^2 a_6^4 \\ &\quad - 2a_2 a_3^2 a_4^3 r^2 - 2a_2 a_3^2 a_4 a_5^2 r^4 + 2a_2 a_3^2 a_4 a_6^2 r^2 + a_3^4 a_4^2 r^4 - 2a_3^2 a_4^2 a_5^2 r^2, \\ b_2 &= a_1^2 a_2^2 r^4 + 2a_1^2 a_2 a_4 r^2 + 2a_1^2 a_4^2 - 2a_1 a_2 a_4 a_5 r^2 + 2a_2^3 a_4 r^4 \\ &\quad + 4a_2^2 a_4^2 r^2 + 2a_2^2 a_5^2 r^4 - 2a_2^2 a_6^2 r^2 - 2a_2 a_3^2 a_4 r^4 + 2a_2, \\ b_3 &= (a_2 r^2 + a_4)^2. \end{aligned}$$

The polynomial (23) always possesses at least one real root for ρ . We now investigate conditions which ensure that it possesses at least one positive root and discard the case $b_0 = 0$, which would lead to a constant solution. Assuming a factorisation of the form

$$b_3(\rho - \rho_1)(\rho - \rho_2)(\rho - \rho_3) = b_3 [\rho^3 - (\rho_1 + \rho_2 + \rho_3)\rho^2 + (\rho_1\rho_2 + \rho_1\rho_3 + \rho_2\rho_3)\rho - \rho_1\rho_2\rho_3],$$

the fact that b_0 and b_3 are positive implies that the product of roots $\rho_1\rho_2\rho_3$ is negative. Hence, the polynomial either has 1 or 3 negative roots. Moreover, if two roots are complex, say $\rho_3 = \bar{\rho}_2$, then

$$\rho_1\rho_2\rho_3 = \rho_1\rho_2\bar{\rho}_2 = \rho_1|\rho_2|^2 < 0 \Rightarrow \rho_1 < 0$$

and the polynomial has no positive root. Hence, for the polynomial to have at least one positive root, its three roots must be real, or equivalently the discriminant of (23) must be positive. As a consequence, the only choice is to have 1 negative root and 2 positive ones. According to Descartes' rule of signs, the series of coefficients of polynomial (23) must exhibit exactly two sign changes, while the series obtained upon setting $x \rightarrow -x$ must have exactly one sign change. This leads to the following proposition.

Proposition 2. *In the generic case $a_2, a_4, a_1 + a_5 \neq 0$, system (17) possesses at least one sinusoidal solution if the discriminant of (23),*

$$\Delta = 18b_0b_1b_2b_3 - 4b_3^3b_0 + b_1^2b_2^2 - 4b_3b_1^3 - 27b_0^2b_2^2$$

is positive and either i) $b_2 < 0$ or ii) $b_2 > 0$ and $b_1 < 0$ or iii) $b_1 = 0$ or $b_2 = 0$ holds.

Moreover, values of z can be obtained directly by eliminating ω from (21) and (22),

$$\begin{aligned}
& 8a_2a_4(a_1 + a_5)r^3 (a_2r^2 + a_4) \eta^3 \\
& -4r^2 \left[a_2r^4 (a_1^2a_2 - a_2^2a_4 - a_2a_5^2 + a_3^2a_4) \right. \\
& \quad + r^2 (a_2^2a_6^2 + a_3^2a_4^2 - a_1^2a_2a_4 - 2a_1a_2a_4a_5 - 2a_2^2a_4^2 - a_2a_4a_5^2) \\
& \quad \left. - a_4 (a_1^2a_4 + a_2a_4^2 - a_2a_6^2 - a_4a_5^2) \right] \eta^2 \\
& -4r \left[a_1a_2(a_2^2 - a_3^2)r^6 + (a_1^3a_2 + 2a_1a_2^2a_4 - a_1a_2a_5^2 + a_2^2a_4a_5 + a_3^2a_4a_5) r^4 \right. \\
& \quad \left. (a_4a_5^3 - a_1^2a_4a_5 + a_1a_2a_4^2 + a_1a_2a_6^2 + 2a_2a_4^2a_5) r^2 + a_4a_5(a_4^2 - a_6^2) \right] \eta \\
& - \left[(a_2^2 - a_3^2)^2 r^8 + 2 (a_1^2a_2^2 - a_1^2a_3^2 + 2a_2^3a_4 + a_2^2a_5^2 - 2a_2a_3^2a_4 + a_3^2a_5^2) r^6 \right. \\
& \quad (a_1^4 + 4a_1^2a_2a_4 - 2a_1^2a_5^2 + 6a_2^2a_4^2 - 2a_2^2a_6^2 + 4a_2a_4a_5^2 - 2a_3^2a_4^2 - 2a_3^2a_6^2 + a_5^4) r^4 \\
& \quad \left. + 2 (a_1^2a_4^2 + a_1^2a_6^2 + 2a_2a_4^3 - 2a_2a_4a_6^2 + a_4^2a_5^2 - a_5^2a_6^2) r^2 + (a_4^2 - a_6^2)^2 \right] = 0, \quad (24)
\end{aligned}$$

where $\eta = \cos z$. Using equations (21) and (22) one can then obtain the points in the positive (τ_1, τ_2) domain where sinusoidal solutions of the form (18) exist. We now give an example using as starting point the linearisation of system (1) in which we introduce the coefficient a_4 .

Example 1. *Physiological parameters for system (1) in the non-diabetic case $\alpha = \beta = \gamma = 1$ were obtained in [11]. Note that in that case $a_4 = 0$ and here we assume that a_4 is sufficiently small and represents a first-order approximation of an instantaneous glucose-dependent insulin release. The corresponding values are given by*

$$a_1 = -0.010, \quad a_2 = -0.855, \quad a_3 = -2.457, \quad a_5 = 0.06, \quad a_6 = 0.001. \quad (25)$$

Following the procedure just highlighted, it can be seen (Figure 13) that for each value of $-1 \leq a_4 \leq 1$, there exists a small range on r for which the conditions of Proposition 2 are satisfied. For example, for $a_1 = 0.00001$, the range of $0.0145619 \leq r \leq 0.0170074$ is determined numerically with corresponding ω 's within $[0.0253264, 0.0471886]$. For each value of r , values of ω and z are obtained from (23) and (24). For each trio (r, ω, z) , equations (20) are then used to obtain the resulting values for τ_1 and τ_2 . Because of the periodicity of these equations, we report here only the minimal positive values of the delays.

Increasing a_4 has a crucial effect of the production of sinusoidal solutions (Figure 14). The lower branch of the graph for $a_4 = 0.00001$ gives an approximation to the transcendental curve of Hopf bifurcations which was presented in Figure 2. The graph in Figure 14 shows that this curve is part of a closed loop in this space. For comparison, increasing a_4 and repeating the analysis shows that it deforms this loop by shrinking it progressively, here represented for $a_4 = 0.1$. We observe numerically that values of a_4 larger than around 39.02 cannot lead to an oscillatory solution. However, in the context

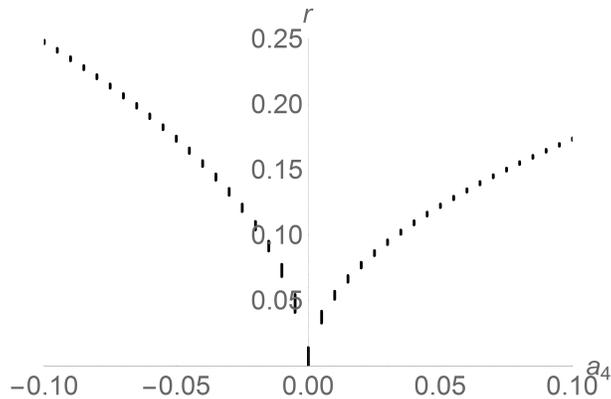


Figure 13: Values of r which satisfy the conditions of Proposition 2 for $a_4 \in [-1, 1]$.

of glucose-insulin regulation, it is reasonable to expect that a value above the delayed insulin production or the degradation rate will break the ability of the system to generate oscillations.

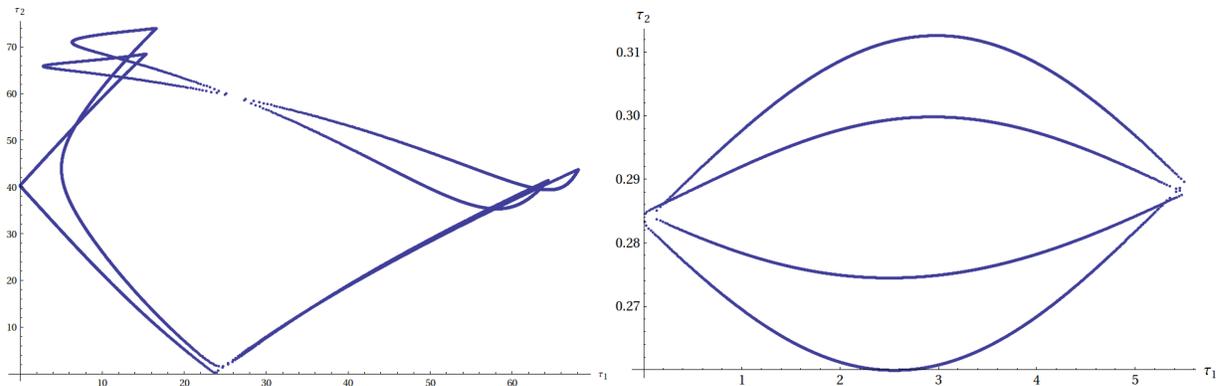


Figure 14: Existence of oscillatory solutions in the (τ_1, τ_2) domain for $a_4 = 0.00001$ (left) and $a_4 = 0.1$ (right). Given the periodicity of equations (20), only the curves which provide the minimal values for τ_2 are reported.

6. Discussion and Conclusions

The theoretical and numerical results obtained in Sections 3 to 5 have highlighted the effect of diabetic deficiencies on the cyclic regulation of glucose in the ultradian regime. The regulatory negative feedback loop, which is modelled by taking into account production times for pancreatic insulin and hepatic glucose, provides an important mechanism for investigating this regulation. On one hand, the model predicts a dampening of the oscillations in the case of a reduced capacity to utilise insulin to degrade glucose. This behaviour was observed in clinical trials involving constant glucose infusions in type 2 diabetic patients [24]. Note that a similar effect of insulin resistance

was also noted on the production of fast oscillations [15] (see also e.g. [22] for a general review of the effect of diabetes on β -cell activity). On the other hand, the usage of the current model has permitted the recovery of healthy regulation through the original objectives: (i) the production an oscillatory regime while (ii) stabilising the average glucose levels within a physiologically acceptable range.

Here we have highlighted the importance of considering variable insulin degradation rates as these have an important effect of the production of an oscillatory regime. By considering the insulin clearance term as a combination of both natural and external mechanisms for the degradation of insulin and combining its effect with other parameters such as insulin sensitivity, pancreatic secretion and hepatic glucose production, four strategies have been investigated in Section 4. We have shown that it is generally possible to individually alter these parameters, either positively or negatively, to stabilise average glucose levels. These alterations take into account current therapeutical pathways, such as insulin infusions and drugs that inhibit hepatic glucose production such as Metformin, which typically only focus on reducing glucose levels. The effect of this manipulation on the generation of oscillations has been investigated. We then established regions in the space of diabetic parameters α and β where both objectives can be achieved. In several cases, it would be worth considering combinations of these strategies in order to deliver an optimal treatment which combines the benefits of having an oscillatory regime within an acceptable range. Splitting the insulin contribution into dynamically linked compartments accounting for plasma and remote insulin with individual transfer and degradation rates, as done in [40], may as well lead to more precise recovery pathways. Such a study is currently under way.

However, at this stage, the qualitative contribution of the strategies described in Section 4 should be considered more important than specific numerical values. One reason for this is that insufficient exhaustive characterisations of the ultradian oscillatory regulation of diabetically-impaired systems are available. Nevertheless, the model appears to be sufficiently robust for qualitatively establishing the effect of diabetic parameters. For instance, adding a 5% white noise to the diabetic parameters does not incur very large variations in the period and amplitude of the oscillatory regime, as shown in Figure 15. Two approaches could be employed in order to strengthen the current proposed pathways and provide a more quantitative framework. Firstly, appropriately designed clinical trials aiming at evaluating variations in oscillatory patterns in subjects at various diabetic states under glucose infusions would be of great value. Secondly, new multiscale simulations taking into account dynamics at the β -cell secretion level as performed in [4] in the case of decreased insulin sensitivity could lead to a further assessment of the current model against clinical observations.

Moreover, we have shown that taking into account an instantaneous glucose-dependent insulin production, through the introduction of an additional coefficient, enables us to characterise the existence of sinusoidal solutions by investigating roots of a cubic polynomial. This provides an additional mean for investigating the curve of Hopf bifurcations, which separates asymptotically stable and oscillatory regimes in system (1), without relying on a transcendental equation. It is numerically evidenced to be part of a closed

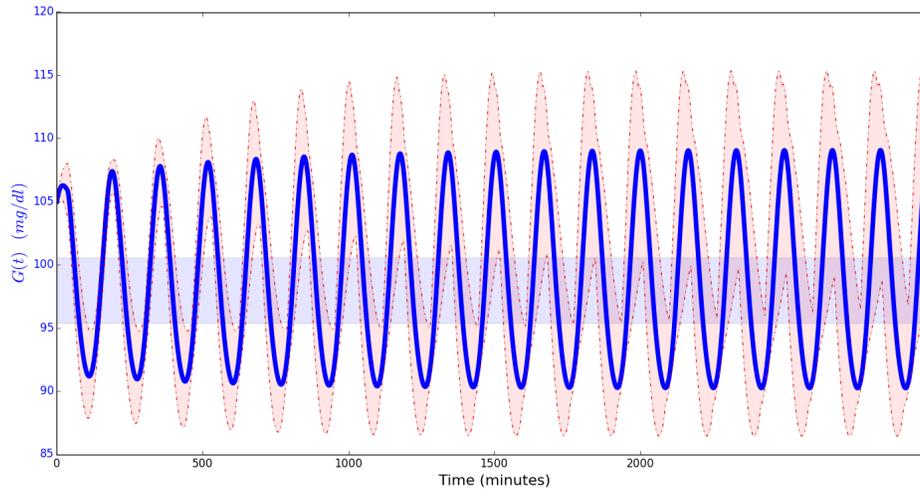


Figure 15: Ultradian oscillations with a 5% noise on α and β around $\alpha = \beta = 1$. The middle band represents the associated variability of G^* . A similar effect can be observed on insulin patterns. Simulation performed with 500 repetitions.

loop in the (τ_1, τ_2) domain.

Finally, in view of the recent efforts for the development of an artificial pancreas, these result open the way for more in-depth analysis of the underlying mechanisms which are most responsible for generating the oscillations. The presence of periodic solutions in the (τ_1, τ_2) can be detected using Proposition 2 and these could be used for further investigation of the mechanisms involved in the oscillatory regulation. In particular, combining strategies discussed in Section 4 may provide additional pathways for reintroducing a physiologically appropriate cyclic regulation and devise new regimes for personalised treatment.

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